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REVIEW

# Biomedical Applications of Quantum Dots: Overview, Challenges, and Clinical Potential

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**Abstract:** Despite the massive advancements in the nanomedicines and their associated research, their translation into clinically-applicable products is still below promises. The latter fact necessitates an in-depth evaluation of the current nanomedicines from a clinical perspective to cope with the challenges hampering their clinical potential. Quantum dots (QDs) are semiconductors-based nanomaterials with numerous biomedical applications such as drug delivery, live imaging, and medical diagnosis, in addition to other applications beyond medicine such as in solar cells. Nevertheless, the power of QDs is still underestimated in clinics. In the current article, we review the status of QDs in literature, their preparation, characterization, and biomedical applications. In addition, the market status and the ongoing clinical trials recruiting QDs are highlighted, with a special focus on the challenges limiting the clinical translation of QDs. Moreover, QDs are technically compared to other commercially-available substitutes. Eventually, we inspire the technical aspects that should be considered to improve the clinical fate of QDs.

**Keywords:** quantum dots, clinical translation, clinical trials, in vivo imaging, photodynamic therapy, biosensors

## Introduction

Nanomedicines have witnessed massive developments and growing interests since late 1990s. According to a recent survey, there have been more than 32,000 publications involving nanomedicines as of 2020. Nevertheless, the rate of translation of nanomedicines from the bench to the clinics is still below premises.[1] The evolution of COVID-19 vaccines based on nanomedicines has rekindled the hope in the power of nanomedicines as a protective tool to rescue the world during the pandemic.[2] The latest evolution has triggered interest in lipid nanoparticles (LNPs) as efficient nanovectors, with a wide diversity of applications.[3–5] However, inorganic nanoparticles represent another interesting category of nanomedicines which is still underestimated. Most inorganic nanoparticles are based on metals, such as silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), metal-organic frameworks (MOFs), and quantum dots (QDs).[6–9] The latter type is a dark area that needs light to be shed on.

QDs are semiconductors-based ultra-small nanocrystals (1–15 nm) with amazing optical properties, which were first reported in 1980s by the physicist, Alexei Ekimov, who devoted his research on semiconductors.[10] According to their chemical composition, QDs can be classified into 12 types based on the position of their composing elements in the periodic table of elements (Table 1). For example, group IV A QDs compose of tetravalent elements such as Carbon, Silicon, and Germanium, which possess four electrons in their outermost shell, and share common physico-chemical features including their metalloid nature and semiconducting electrical properties.[11] The vast majority of QDs share a common chemical composition of a heavy metal core surrounded by a bandgap semiconductor shell, such as CdTe, PbSe, ZnSe, or CdS core materials surrounded by $SiO_2$ shell, which overcomes the surface deficiency and increases the

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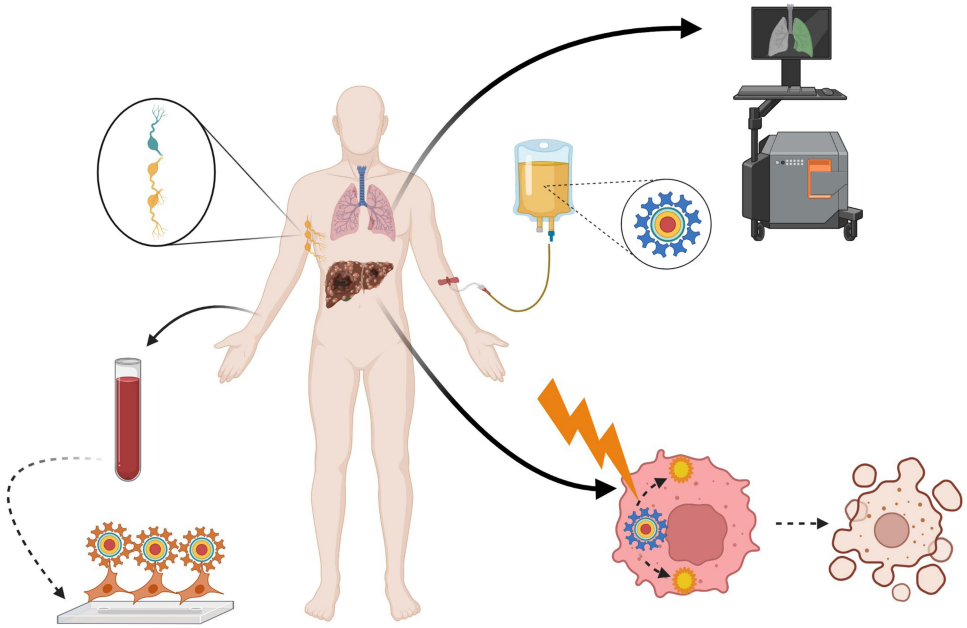
**Graphical Abstract**



quantum yield.[9,12] Exceptions from this common composition include QDs based on a single semiconductor element such as Si QDs, or QDs based on semiconducting polymers (P dots). Chen et al synthesized P dots based on a novel semiconducting polymer called NIR800, which emits light in the near infrared region (~800 nm), facilitating interesting biological applications including flow cytometry and in vivo imaging.[13]

Generally, QDs have interesting features including small particle size, tunable composition and properties, high quantum yield, high brightness, and intermittent light emission (blinking), which have recruited them in versatile applications such as solar cells, LED technology, and biomedical applications including imaging, drug delivery, and cancer photodynamic therapy.[14–16] The tunable optical properties of QDs can be considered the major attractive feature

**Table 1** Classification of QDs According to Their Chemical Composition

| Type | Examples | Reference(s) |
|---|---|---|
| I B-VI A | $Cu_2S$ | [9] |
| I B-VII A | AgBr | [121] |
| II B-VI A | ZnSe, ZnS, ZnO, CdS, CdSe, CdTe, HgS | [122] |
| III A-V A | AlSb, AlAs, AlP, GaSb, GaAs, InAs, InP | [9] |
| IV A-VI A | PbS, PbSe, PbTe | [123] |
| IV A | C, Si, Graphene | [124] |
| V A | Black Phosphorus | [125] |
| I B-III A-VI A | $CuInS_2$, $CuInSe_2$, AgInS | [9] |
| P dots | NIR800 | [13] |
| TMDCs | $TiSe_2$, $TaS_2$, MoSe2 | [126] |
| MXene[a] | $Nb_2C$, $Ti_3C_2$ | [127,128] |
| Perovskite[b] | CsPbI3 | [129] |

**Notes**: [a]MXene QDs usually exist in the chemical form $M_{n+1}X_n$ or $M_{n+1}X_nT_z$ where M = transition metals; X = C and/or N; *n* = 1–3; Tz = $F^-$, $O^{-2}$, and $OH^-$. [b]Perovskite QDs are QDs with a crystal structure similar to the mineral salt, $CaTiO_3$. They usually exist in the chemical form $MPbX_3$, where M = Cs or CH3NH3; X = Cl, Br, or I.
**Abbreviations**: P dots, semiconducting polymer dots; TMDCs, transition metal dichalcogenides.

of them. Thanks to the very small size of QDs, they behave like single atoms in contrary with the bulk semiconductors. In the ultra-small QDs, the electron energy levels are well-separated rather than being semi-continuous like in classic semiconductors. The latter fact results in "quantum confinement" phenomenon, in which the band gap energy (ie the energy required to excite an electron from the low-energy valence band to the high-energy conduction band) is relatively-high owing to the compact atom-like nature of QDs. The smaller the size of QDs is, a higher band gap energy is required, which increases the energy of the emission photon, with subsequent shortening of the emission wavelength, and vice versa. Therefore, the optical performance of QDs is size-dependent more than being material-dependent, which can be exploited to manipulate their electromagnetic radiation from the UV region up to the far infrared region via controlling the particle size.[17,18] In addition, QDs demonstrate a prominent "Stokes shift" phenomenon resulting in a good separation between the shorter-wavelength excitation spectra and the longer-wavelength emission spectra, with a subsequent improvement in the detection sensitivity and reduction in the optical overlap.[19,20] Some applications of these unique optical properties and their manipulation are discussed in subsequent sections of this article.

Despite these promising characteristics, QDs are still far from the clinics, with a limited number of ongoing clinical trials. In the current article, we highlight the shortcomings of QDs and discuss the challenges associated with their clinical translation, with the purpose of inspiring potential approaches to tackle these drawbacks. First, we review the recent methods for the preparation and characterization of QDs to understand the basic obstacles related to their production. Then, we discuss some biomedical applications of QDs, their status in the healthcare market, the ongoing clinical trials involving QDs and their associated challenges, as well as a technical comparison of QDs to other commercially-available substitutes. Eventually, we highlight some promising applications that can bring QDs to the clinics and identify the essential considerations to improve their clinical fate.

# Preparation and Characterization of QDs

## Preparation of QDs

The basic concept for most preparation methods of QDs is to assemble their precursors in the molecular state into nanocrystals, which form the QDs (bottom-up approach).[21] This can be rendered by a variety of physical and chemical approaches. In this section, we highlight some promising methods for the preparation of QDs in terms of their uniformity, reproducibility, and scalability. These can be classified into four fundamental approaches: colloidal synthesis, biotemplate-based synthesis, electrochemical assembly, and biogenic synthesis, which are illustrated in Figure 1.

Colloidal synthesis is considered one of the most established and popular methods for the preparation of QDs.[9] The principle depends on the injection of the precursor metals into a solvent under high temperature to render them to the molecular state. Then, the precursor molecules assemble into nuclei (nucleation step) which subsequently grow into nanocrystals (crystal growth step). The latter step plays a pivotal role in tuning the physico-chemical properties of the produced QDs. After reaching the desired particle size, the crystallization reaction is terminated and QDs are retrieved from the solvent (termination step).[22] The solvents used in this reaction are mostly of organic nature, thus this method is also described in literature as organometallic synthesis.[22,23] Examples of QDs prepared by this method include CdTe/CdS and PbS QDs.[23,24] Organometallic synthesis produces QDs with high monodispersity, high quantum yield, and narrow peak emission, which collectively qualify them as excellent candidates for imaging applications. However, the presence of organic solvents in this method increases the risks associated with residual solvent in terms of stability and toxicity.[25] In addition, QDs prepared by this method are usually capped with hydrophobic ligands which necessitates post-synthesis modifications of the prepared QDs to impart aqueous solubility such as exchange with hydrophilic ligands (eg thiolated compounds), polymeric coating (eg amphiphilic block copolymers), or modification with silica-based shells.[9,26] Despite the efficiency of the aforementioned modifications, they increase the complexity of the production, with a subsequent impact on the scalability and production costs. The recruitment of aqueous solvents in replacement of organic ones has emerged to tackle the above shortcomings.[27] Several QDs were prepared using aqueous solvent-based synthesis including $CuInS_2$ QDs, CdS QDs, $AgInS_2$–ZnS QDs, and ZnSe QDs.[28] Aqueous-based synthesis produces smaller QDs (average particle diameter < 5 nm) and eliminates the necessity for post-synthesis solubilization

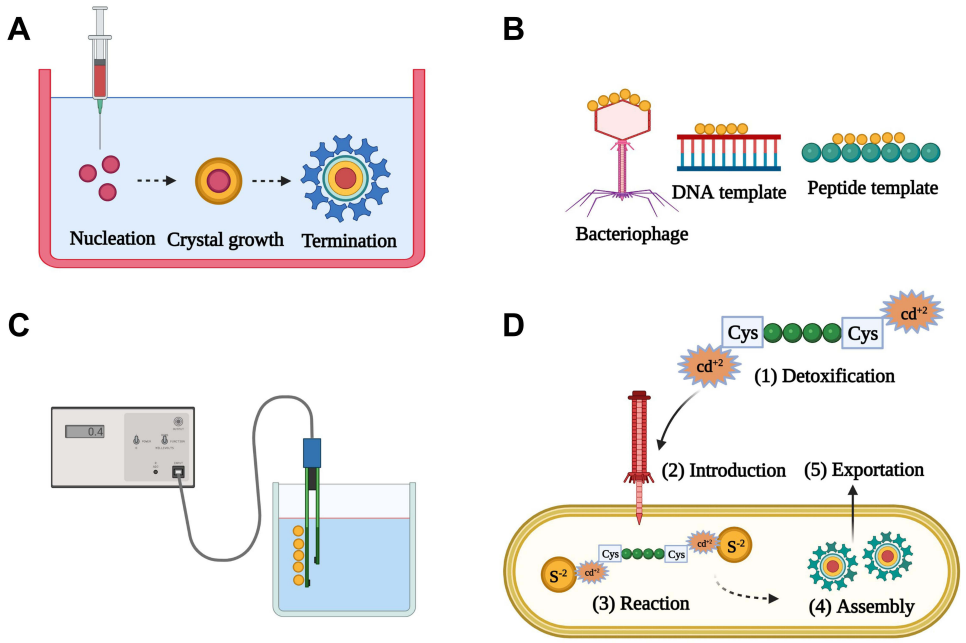



**Figure 1** A scheme of some commonly-used methods for the preparation of QDs. (**A**) Colloidal synthesis. Precursors are injected into organic or aqueous system under high temperature to facilitate their conversion into the molecular state, with a subsequent assembly into QDs. The major reaction steps include nucleation, crystal growth, and termination, which can be manipulated to control the physico-chemical properties of the produced QDs. (**B**) Biotemplate-based synthesis. Biological entities such as bacteriophages, genetically-engineered viruses, DNA, or peptides are used as templates to assemble the precursors into QDs. (**C**) Electrochemical assembly. Electrochemical driving force is used to assemble the precursor ions into QDs at the electrolyte-metal interface. (**D**) Biogenic synthesis. Heavy metal ions are detoxified via binding to cysteine-terminated peptides, followed by their introduction into microorganisms such as *E. coli*, where they react with the endogenous co-precursors (eg, sulfide ions) and assemble into QDs, which are subsequently exported out of the microorganism. Created by BioRender.com.

approaches.[27] Nevertheless, the produced QDs demonstrate poor optical properties compared to those produced with organometallic synthesis.[9]

Biotemplate-based synthesis is a novel approach for the preparation of various crystals of pharmaceutical interest, including QDs. Biomacromolecules such as DNA, RNA, peptides, or viruses such as bacteriophages are used as biosurfaces for the assembly of precursor molecules into QDs. The application of such biotemplates has enabled precise control of the size, morphology, and optical properties of the produced QDs, in addition to imparting better stability and solubility.[9,29] An example of such a synthesis was presented by Kasotakis et al, who assembled CdSe@ZnS core–shell QDs on peptide-based templates. The prepared QDs demonstrated a significant red shift in their emission spectra owing to the synergistic interaction between the adjacent QDs arranged on the peptide template.[30] On the other hand, the application of biotemplates necessitates operation at mild reaction conditions, which may reduce the optical properties of the produced QDs.[31,32]

Electrochemical synthesis is an additional approach for the preparation of QDs, in which electrochemical forces are used to drive the assembly of precursor molecules into QDs. The size of the produced QDs can be manipulated via the applied potential, redox time, and concentration of the supporting electrolyte. In a recent study, Kalita et al fabricated graphene QDs from graphene oxide at room temperature using $LiClO_4$ in propylene carbonate as an electrolyte. The resultant QDs had an average diameter of 3–5 nm and were applied as sensors for the soil moisture.[33]

Biogenic synthesis is a novel biotechnology-based approach for the scalable production of QDs. In this approach, living microorganisms such as *E. coli* are exploited as bioreactors for the synthesis of QDs like CdS. The first step includes the detoxification of cadmium ions, that are detrimental to living organisms, via their conjugation to cysteine-terminated peptides. Then, the detoxified ions are introduced into the bacteria where they react with the endogenous sulfide ions and assemble into CdS QDs that are eventually exported outside the bacteria and retrieved. This approach holds several promises including environmental tolerability, biosafety, economic production, and scalability. Moreover, the composition of the peptide used during the detoxification step can manipulate the physico-chemical properties of the resultant QDs.[34,35]

## Characterization of QDs

The particle size of QDs plays a pivotal role in determining their optical properties. Therefore, the accurate determination of the particle size is a critical step in the characterization of QDs. Dynamic light scattering (DLS) is a fundamental technique that is widely used in the characterization of various nanomedicines. However, considering the ultra-fine nature of QDs, more sensitive and reliable techniques should be applied. Electron microscopy technologies including scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) are widely applied for the accurate determination of the particle size of QDs, in addition to their morphology and internal composition.[36] In addition, photoluminescence and Raman scattering spectroscopies can be used to investigate the particle size and composition of QDs, exploiting their inherent optical properties.[37] Moreover, Lees et al reported that the surface chemistry of QDs contributes to their final hydrodynamic diameters. Various methods can be used to study the surface chemistry of QDs including X-ray photoelectron spectroscopy, nuclear magnetic resonance spectroscopy, Rutherford backscattering, and analytical ultracentrifugation.[38] Meanwhile, the optical properties of QDs are commonly investigated via UV-VIS and photoluminescence spectroscopies to determine their excitation and emission spectra as well as quantum yield and brightness.[36] Thanks to their excellent optical properties, QDs can be easily tracked intracellularly via fluorescence-based microscopic technologies such as fluorescence microscopy and confocal laser scanning microscopy (CLSM).[39] Furthermore, the biodistribution of QDs in experimental animals can be visualized by various in vivo imaging systems (IVIS).[40]

# Biomedical Applications of QDs

## Live Cell Imaging and in vivo Imaging

QDs have amazing optical properties including high quantum yield, high brightness, high extinction coefficient, high stability against photobleaching, and intermittent fluorescence signals (blinking).[9,41] In addition, it has been found that the emission spectra of QDs are correlated with their particle diameters, thus enabling tuned optical properties via the manipulation of the particle size.[42] For example, CdSe QDs can emit fluorescence at various regions in the visible range (400–600 nm) via manipulating their particle size from 2–10 nm. It has been reported that the emission wavelength is directly proportional to the average particle diameter (Figure 2).[43] Moreover, both the particle size and emission spectra of QDs can be tailored through the manipulation of the core composition. For example, QDs with CdS core possess an average particle diameter of 1–6 nm and demonstrate emission spectra in the ultraviolet-visible (UV-VIS) range depending on the particle size. Meanwhile, QDs with InAs core owe comparable particle diameters, but demonstrate emission spectra in the infrared (IR) region. Additional examples for the impact of the core composition on the particle size and emission spectra of QDs are listed in Table 2.[44] The above features have led to the wide application of QDs as excellent fluorescent probes for diverse type of biomedical imaging.[45] On the cellular level, QDs are used for visualization of the intracellular components. Upon incubation of QDs with the desired cells, QDs are readily taken up by the cells thanks to their fine particle size. Subsequently, they can be excited and the emission spectra can be easily detected by fluorescence microscopes or CLSM (Figure 3A). The unique blinking feature of QDs facilitates the detection of a single QD event, with a subsequent capability of visualizing individual subcellular components such as proteins, unlike other conventional fluorescent probes with continuous fluorescence emission.[46] Furthermore, QDs are also applied in the in vivo visualization of various organs and tissues, following administration of QDs that are functionalized with certain ligands to increase their affinity to the organs or tissues of interest (Figure 3B).[47]

## Fluorescence-Activated Cell Sorting (FACS)

FACS is a widely-used technology for a wide diversity of biomedical applications including evaluation of the cellular uptake of drug delivery systems, isolation of distinct cell populations, characterization of certain diseases models, detection of cellular markers, and mapping of immune cells.[5,48,49] QDs possess high potential to be applied as fluorescent labels in FACS (Figure 3C) thanks to several features. Compared to the currently-used organic dyes, QDs have narrow emission spectra which reduces overlapping and increases the possibility of including multiple labels for polychromatic cell sorting by FACS. On the contrary, their broad excitation spectra facilitate the recruitment of a single laser beam for the excitation of multiple QDs probes, which increases the individual capabilities of FACS equipment.[50] In addition, QDs

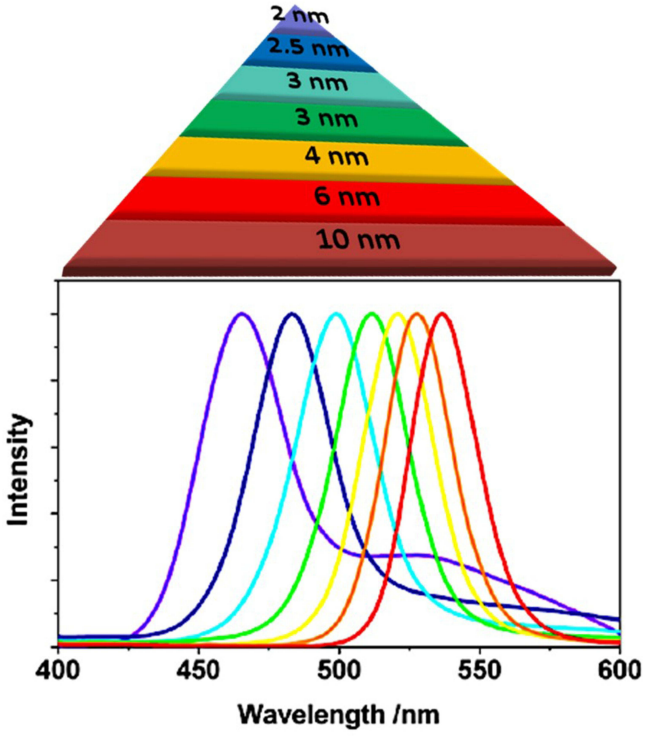



**Figure 2** Impact of the particle size of CdSe QDs on their emission spectra upon irradiation with UV light. The emission wavelength is directly proportional to the particle size. Adapted from *Bera D, Qian L, Tseng T-K, Holloway PH. Quantum Dots and Their Multimodal Applications: A Review. 2010;3(4):2260–2345.*Copyright © 2010 by the authors; licensee Molecular Diversity Preservation International, Basel, Switzerland. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).[43]

demonstrate higher brightness compared to most organic dyes, which increases the detection accuracy.[51] Filho et al applied CdTe QDs as fluorescent probes conjugated to monoclonal antibodies against A and B antigens on the surface of red blood corpuscles (RBCs) for studying blood groups by FACS. The bioconjugate demonstrated high efficiency and was stable over 6 months.[52] Moreover, QDs hold the potential to replace the antibodies that are commonly used for staining cell surface markers thanks to their higher stability and economic prices, if they are to be functionalized with specific targeting ligands to recognize the target markers. Unlike antibodies, QDs can be readily taken up by the cells enabling the staining of intracellular markers and eliminating the need for permeabilization buffers that affect cell viability, fluorophore efficacy, and increase the complexity of FACS experiments.[53]

**Table 2** Impact of Core Composition on the Particle Size and Emission Spectra of QDs.[44]

| Core Composition | Size Range (nm) | Emission Range |
|---|---|---|
| CdSe | ≈1.0–25 | Visible |
| CdS | ≈1.0–6.0 | UV, Visible (size-dependent) |
| CdTe | ≈1.0–8.0 | Visible |
| ZnSe | ≈4.3–6.0 | UV, Visible (size-dependent) |
| ZnSe: Mn | ≈2.7–6.3 | UV, Visible (size-dependent) |
| GaP | ≈2.0–3.0 | UV, Visible (size-dependent) |
| $GaInP_2$ | ≈2.5–6.5 | UV, Visible (size-dependent) |
| InP | ≈2.6–6.0 | UV, Visible, Near IR (size-dependent) |
| InAs | ≈2.8–6.0 | IR |
| PbSe | ≈3.0–12 | Near/mid-IR (size-dependent) |
| SnTe | ≈4.5–15 | Mid-IR |

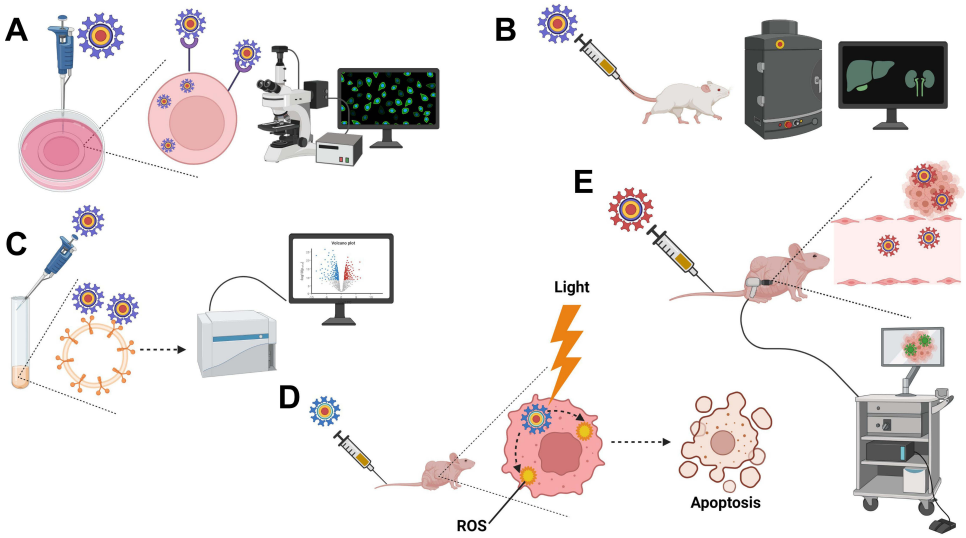



**Figure 3** Some biomedical applications of QDs. (**A**) Intracellular imaging. QDs decorated with specific targeting moieties are used as fluorescent labels for intracellular visualization by fluorescence microscopy or confocal laser scanning microscopy (CLSM). (**B**) In vivo imaging. Following administration, QDs modified with tissue-specific targeting moieties can be used for visualization of certain organs in question using in vivo imaging systems (IVIS). (**C**) Fluorescence-activated cell sorting (FACS). QDs decorated with cell-specific ligands can be used as fluorescent probes for cell sorting during flow cytometry. Thanks to numerous advantages, QDs have a better capacity in polychromatic cell sorting compared to conventional organic dyes. (**D**) Photodynamic therapy (PDT). Following irradiation, QDs can act as photosensitizers or energy donors to other photosensitizers to generate reactive oxygen species (ROS) in situ leading to apoptotic cell death during cancer treatment. (**E**) Traceable drug delivery vehicles. QDs can be used as drug carriers to various tissues with high extravasation and tissue penetration capabilities thanks to their ultra-fine particle sizes. Owing to their quantum properties, QDs accumulation in the target tissues can be easily tracked. Created by BioRender.com.

## Photodynamic Therapy (PDT)

PDT has been introduced as a promising strategy for the treatment of various cancers including skin, head and neck, tongue, and breast cancers.[54] In this strategy, a chemical compound called photosensitizer is activated by light irradiation to transfer energy to the intracellular molecular oxygen leading to the in situ generation of reactive oxygen species (ROS), with subsequent induction of apoptosis in the target tumor cells.[55] In such an area, QDs have the ability to act both as photosensitizers or energy donors for other photosensitizers. QDs have numerous advantages compared to organic photosensitizers including potent light absorption, strong emission, high photostability, water solubility, tuned optical properties, and high tissue accumulation. In addition, the size and composition of QDs can be manipulated to optimize the emission in the near infrared (NIR) region, which demonstrates strong tissue penetration that is suitable for the treatment of deep-sited tumors. The principle of the application of QDs in PDT is schemed in Figure 3D. In a recent study, Ahirwar et al investigated the potential of graphene QDs (GQDs) and graphene oxide QDs (GOQDs) as photosensitizers for cancer PDT. Upon irradiation of the QDs by 290 μW power UV tubelight, QDs could kill 90% of B16F10 melanoma cells and MCF-7 breast cancer cells within only 5 minutes, revealing high potency and efficiency.[56] Moreover, recent reports suggested that carbon QDs hold the promise to be used in the PDT of COVID-19 via a dual mechanism of ROS generation and type I interferon response stimulation.[57,58]

## Traceable Drug Delivery

In addition to their optical properties applicable in bioimaging and PDT, QDs can be used as drug delivery vectors as well. QDs have multiple attractive features as drug delivery systems including their ease of fabrication, capability of conjugation to a wide variety of drugs, tuned physico-chemical properties, and interesting optical properties making them traceable drug carriers that can be easily monitored after administration.[9,59] Furthermore, the ultra-small particle size of nanocarriers is an essential feature required for extravasation and penetration through the stroma-rich microenvironment of challenging tumors such as hepatocellular carcinoma and pancreatic cancer.[4,60] In the latter case, QDs with their sub 10 nm particle size hold a great promise as tumor-penetrating delivery vectors.[61] The principle of using QDs in traceable drug delivery to the tumors is illustrated in Figure 3E.

Moreover, QDs are feasible for diverse physical and chemical modifications such as decoration with targeting ligands or functional coatings to modulate their biodistribution and pharmacokinetic properties. PEGylation is usually used to improve the retention time in the blood circulation following intravenous administration, which is essential to achieve substantial tumor accumulation required for cancer therapy.[1,62] Folic acid is a widely-used ligand to target the over-expressed folate receptors on the surface of cancer cells.[63–65] In a recent study, Abdellatif et al functionalized Cd/Se QDs with vapreotide as an agonist for somatostatin receptors in blood cells, with the potential of treating blood cancers.[66] In another study, Liu et al prepared doxorubicin-loaded PEGylated $MoS_2$ QDs for traceable delivery of doxorubicin to cancer cells. The prepared QDs exhibited blue photoluminescence and pH-responsive drug release, while demonstrating good stability and biosafety under physiological conditions.[67] Additional examples of functional surface modifications of QDs are summarized in Table 3.

Functionalized QDs are often taken up by the cells via receptor-mediated endocytosis. Under receptor-mediated endocytosis, there are three common pathways by which the cells react with the ligand-modified QDs, which are schemed in Figure 4. The nature of the used ligand, target receptor, and composition of the QDs determine their endocytic fate.[68,69] In clathrin-mediated endocytosis, the nanoparticles concentrate at the target receptor site, where they are engulfed by the cell membrane that is coated with a protein, clathrin, to form clathrin-coated vesicles. The membrane protein, dynamin, subsequently mediates the dissociation of these vesicles from the cell membrane into the cytoplasm, with the formation of endosomes. If QDs can escape from endosome, they will be released into the cytosol and become accessible to exert their action and release their cargos. Otherwise, they will suffer lysosomal degradation. In caveolae-mediated endocytosis, the binding of the functionalized particles to their receptors mediates their internalization into the target cells via cholesterol-rich flask-shaped membrane invaginations, called caveolae, which subsequently dissociate from the cell membrane, forming caveosomes. Caveosomes are thought to be less-destructive vesicles compared to endosomes, which is beneficial to maximize the drug delivery efficiency to the target cells. In macropinocytosis, certain ligands can trigger the formation of cell membrane ruffles that engulf the particle into the cytosol, forming macropinosomes, which subsequently leak their cargo into the cytosol.[70]

## QDs in Biosensors; the Integration of Efficiency and Selectivity

In addition to the above-mentioned applications, QDs have gained interest in the area of biosensors.[71] Biosensors are systems that can produce a measurable signal in response to the biological process in question. Biosensor systems depend basically on the selectivity of the system to the target molecule(s), where click chemistry, bioresponsive polymers, antibodies, ligands, or artificial receptors are applied to impart selectivity.[72] Thanks to the excellent and unique optical properties of QDs, they can be incorporated into such biosensor systems to integrate selectivity, efficiency, accuracy, and high detection sensitivity into a single system. QDs-containing biosensors can be applied in a wide diversity of

**Table 3** Examples of Functional Surface Modifications of QDs and Their Applications

| Core/Multilayer Shell | Surface Modification | Target Receptor | References |
|---|---|---|---|
| CdSe/CdS/ZnS QDs | Folic acid | Folate receptors | [63] |
| Graphene QDs (GQDs) | Anti-EGFR antibody | EGFR | [130] |
| Cd/Se | Aptamer 32 | EGFRVIII in glioma cells | [131] |
| CdSe/ZnS | Dendrimer linked to PEG-folate | Folate receptors | [64] |
| Cd/Se QDs | PEG-Folic acid | Folate receptors | [65] |
| CdSe/ZnS | Peptide E5 | Chemokine receptor 4 | [132] |
| Gold QDs (AuQDs) | Cold atmospheric plasma | Fas/TRAIL-mediated cell death receptor | [133] |
| Carbon QDs (CQDs) | Retinoic acid receptor responder protein 2 | Retinoic acid receptor | [134] |
| Cd/Se | Anti-VEGFR Antibodies | VEGFR | [135] |
| Cd/Se | Vapreotide | Somatostatin receptors | [66,107] |
| $Ag_2S$ QDs | ZEGFR1907 antibody | EGFR | [136] |
| GQDs | Reduced graphene | Aryl hydrocarbon receptor | [137] |
| Cd/Se | Synaptic proteins | Neurotransmitter receptors | [138] |

**Abbreviations**: EGFR, epidermal growth factor receptor; PEG, polyethylene glycol; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

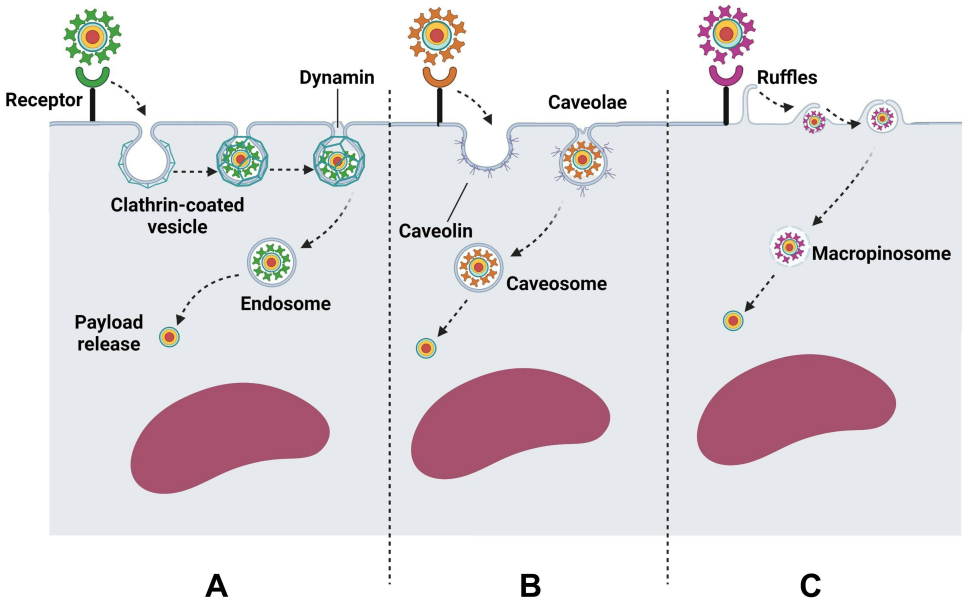



**Figure 4** Some common routes by which functionalized QDs internalize into the target cells. (**A**) Clathrin-mediated endocytosis. Following concentration of QDs at the receptor region, QDs are engulfed into clathrin-coated cell membrane invaginations, forming clathrin-coated vesicles. Dynamin mediates the dissociation of the aforementioned vesicles from the cell membrane into the cytosol leading to the formation of endosome. Subsequently, QDs should escape from the endosome and be released into the cytosol to avoid lysosomal degradation. (**B**) Caveolae-mediated endocytosis. The bindings of functionalized QDs to certain receptors mediates their internalization into the target cells via cholesterol-rich flask-shaped membrane invaginations, called caveolae, which subsequently dissociate from the cell membrane, forming caveosomes. Caveosomes are thought to be less destructive than endosomes. (**C**) Macropinocytosis. The binding of functionalized QDs to certain receptors activates the formation of cell membrane ruffles that engulf QDs into the cytosol forming macropinosomes, which subsequently leak their cargo into the cytosol. Created by BioRender.com.

diagnostic, toxicological, and follow-up medical applications.[73,74] In addition, QDs-based sensors have been applied extensively in environmental applications such as detection of water and soil contamination, which are beyond the scope of the current article.[75]

In the area of vital biochemical markers, Shen and Xia synthesized carbon QDs (CQDs) modified with boronic acid moieties as biosensors for the measurement of the blood glucose level. Upon reaction with glucose-containing blood, boronic acid functionalities intercalate with the glucose molecules inducing the aggregation of CQDs, with a subsequent quenching of their fluorescence. The resultant quenching is a function of the investigated glucose concentration, with a limit of detection as low as 1.5 μM.[76] In another area, Nideep et al designed pH biosensor based on CdTe QDs capped with mercaptosuccinic acid (MSA) for fluorescence-based pH measurement within the range of 3–11.[77] Zhang and Chen fabricated a hybrid biosensor system based on ZnS: Mn QDs/ mesoporous silica/molecularly imprinted polymer (QD/ MS/MIP) for the therapeutic monitoring of the antibiotic, tetracycline, in serum samples via a linear quenching of fluorescence intensity upon binding the target compound.[78] Numerous similar approaches have been developed for the estimation of other antibiotics including quinolones, amoxicillin, cephalexin, and streptomycin.[79] In the area of diagnostics, Özcan et al integrated Graphene Quantum Dots (GQDs) and multi-Walled Carbon Nanotubes (CNTs) for the quantification of the inflammatory and protumorous marker, interleukin-6 (IL-6), in biological samples.[80] Wang et al developed a QDs-based method for the clinical detection of lung cancer micrometastases in the blood, which is further discussed in section 6.[81] Furthermore, QDs-based biosensors have been applied in toxicological applications. Elmizadeh et al designed a biosensor for the detection of digitalis toxin (digoxin) in the biological fluids. Reduced graphene QDs (rGQDs) were linked to DX aptamer as a source of selectivity. In one approach, the binding of digoxin to the system resulted in a linear quenching of the fluorescence intensity. In another approach, the system's fluorescence was turned off through oxidizing CNTs-mediated fluorescence resonance energy transfer (FRET). Upon binding digoxin, the fluorescence could be recovered via inhibiting the connection between the system and CNTs. The latter approach proved to be more accurate, sensitive, and reproducible.[82]

# QDs in the Healthcare Market: Status, Clinical Profile, and the Associated Challenges

## QDs in the Healthcare Market

The global market of QDs has been estimated to value USD 4 billion in 2021 and it has been forecasted to grow up to USD 8.6 billion in the upcoming 5 years. Although display devices and LED applications have dominated such a market, there has been an increasing interest in the biomedical applications of QDs.[83] In the current subsection, we try to highlight the key market players and some of their innovations for biomedical applications of QDs.

NANOCO™ is a major player in the healthcare market of QDs, with an addressable market size of USD 1 billion in 2022 according to the company's forecast. HEATWAVE™ is an example of NANOCO's marketed products based on QDs technology for biosensor medical applications. This device can be operated within a broad range of electromagnetic spectrum (400–1650 nm) for the non-invasive quantification of interesting biomolecules in the human blood including hemoglobin (at 575 nm), bilirubin (at 455 nm), and glucose (at 1650 nm). VIVODOTS® is another marketed product, in which QDs are applied for the intraoperative mapping of tumorous tissues and avoidance of the unnecessary removal of unaffected tissues.[84]

NN-Labs® is another market player owned by NNCrystal US Corporation™. Products of biomedical interest include both cadmium-based and cadmium-free QDs for cellular imaging, in vivo imaging, and as probes for molecular labelling.[85]

QD LASER™ is a Japan-based developer of QDs for industrial and medical applications. An interesting innovation by the company, called VISIRIUM® Technology, was developed as 50 g-weight eyeglasses which projects images onto the retina to assist people with visual disorders.[86]

## Clinical Profile of QDs

Despite the interesting features of QDs and their versatile applications, the rate of clinical translation of such a technology is still slow. According to the National Institute of Health (NIH) database, there are only 6 registered clinical trials involving QDs as of December 2021, which are listed in Table 4.[87]

In a Phase I clinical trial lead by Abdellatif, CdS/ZnS core-shell type QDs that are carboxylic acid-functionalized (QDs-COOH) were conjugated to veldoreotide as a selective ligand to somatostatin receptors. These QDs were introduced into topical cream for potential bioimaging and anticancer applications in breast and skin cancers.[88] In another trial, Graphene QDs modified with anti-cTnI antibodies in combination with Si nanowire were investigated as photoelectrochemical immunosensor for detecting the concentration of cardiac troponin I (cTnI), a biomarker that is highly associated with acute myocardial infarction, with a potential application as an early diagnostic tool.[89] In the remaining trials, QDs were applied as an immunologic monitoring tool for the clinical evaluation of proposed therapies/vaccines against type I Diabetes Mellitus, where QDs were used to detect specific autoantigen tolerance via the detection of CD8+ autoreactive T cells.[87]

**Table 4** Clinical Trials Recruiting QDs as of December 2021[87]

| NIH Identifier | Phase | Condition(s) | Application |
|---|---|---|---|
| NCT04138342 | Phase I | Breast cancer, skin cancer | Bioimaging/anticancer |
| NCT04390490 | N/A[a] | Acute Myocardial Infarction | Diagnostic Photoelectrochemical immunosensor |
| NCT03895437 | Phase II | Diabetes Mellitus, Type I | Immunologic detection of specific autoantigen tolerance |
| NCT03794973 | Phase II | Diabetes Mellitus, Type I | Immunologic detection of specific autoantigen tolerance |
| NCT03794960 | Phase II | Diabetes Mellitus, Type I | Immunologic detection of specific autoantigen tolerance |
| NCT04590872 | Phase I | Diabetes Mellitus, Type I | Detection of CD8+ autoreactive T cells |

**Notes**: [a]N/A, non-applicable.

## Challenges Hampering the Clinical Translation of QDs

The limited number of clinical trials involving QDs can be attributed to the complex challenges associated with them from pharmaceutical, industrial, technical, and biological aspects, which are summarized in Figure 5 and discussed below.

### Pharmaceutical Issues

From a pharmaceutical scope, QDs are ultra-fine colloidal particles with a massive surface area and a metallic nature, leaving them susceptible to aggregation, degradation, hygroscopicity, or chemical redox alterations. Any slight changes in the physico-chemical properties of QDs can lead to a dramatic impact on their optical properties.[90,91] Tremendous efforts have been exerted to improve the physical and chemical stability of QDs. Zhang et al proposed a chemical method for stabilization of PbS QDs that are susceptible to degradation through the oxidation of surface chalcogen atoms. An in situ surface reaction involving trioctylphosphine was used for passivation of surface S atoms with lead mono-carboxylate. The proposed method effectively protected QDs from oxygen and improved their quantum properties irrespective of the particle size or the original surface ligands.[92] In another approach, CdSe/ZnCdS core/shell QDs as well as InP/ZnSeS core/shell QDs were protected from heat and oxidation via coating with a cross-linked double polymeric shell of thiol-terminated poly(methyl methacrylate-b-glycidyl methacrylate) (P(MMA-b-GMA)-SH) block copolymer ligands. The outer shell was formed of transparent PMMA that did not interfere with the optical properties of QDs, while the inner cross-linked shell imparted protection against oxidation.[93] An additional problem of poor aqueous solubility arises if organometallic synthesis, a highly-productive and a widely-used technique, is adopted for the preparation of QDs. Exchange of surface hydrophobic ligands with hydrophilic thiol-containing compounds, coating with hydrophilic shells, as well as aqueous-based synthesis are suggested solutions that have been discussed previously.[9]

### Industrial Issues

Upon shifting from the laboratory scale to the large-scale production, QDs encounter several industrial drawbacks. First, the multiple surface modifications that are essential for modulating their performance make the mass production of QDs too intricate and a multi-step process.[94] Second, it is difficult to maintain uniform physico-chemical properties of QDs on

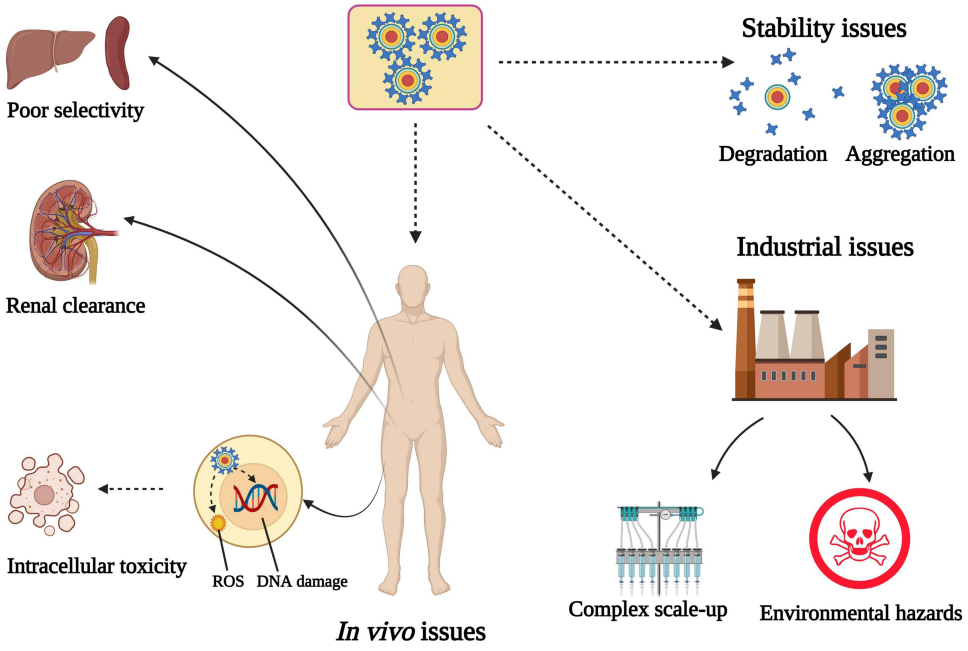



**Figure 5** Common challenges hampering the clinical translation of QDs. Stability issues include the high liability for degradation and aggregation during storage. Industrial issues arise from the complex scale-up procedures and the environmental hazards rendered by the heavy metal components. In vivo issues include the substantial loss of the injected dose via renal clearance owing to the ultra-fine particle size, poor selectivity due to non-specific interactions with tissues and cellular membranes, and intracellular toxicity caused by the generation of ROS or DNA damage. Created by BioRender.com.
**Abbreviation**: ROS, reactive oxygen species.

large scale. Third, traces of impurities in the constituting materials or solvents, that have a negligible effect on the small scale, are also scaled up, exerting a serious impact on the quality and performance of the produced QDs.[95] Peng et al found that alkyl phosphonic and phosphinic acids impurities in trioctylphosphine oxide (TOPO), that is used as a coordinating solvent, play a dramatic role on the performance of CdSe QDs upon scale-up, leading to poor optical performance.[96] Advances in synthesis and purification methods have emerged to tackle the above challenges. Yuan et al reported that the classic hot injection method for the synthesis of CdSe QDs faces difficulties upon scale-up while the injection speed and stirring velocities affect the particle size distribution and subsequently, the optical properties of the resultant QDs. To tackle this challenge, they developed a one-pot strategy in which precursors are mixed together at room temperature, and then all reaction components are heated uniformly. The developed method was injection-free, robust, and demonstrated comparable optical properties to QDs produced by the classic method, with a superiority in scale-up.[95] Steckel et al fabricated PbS QDs on industrial scale using a novel electrochemical method, where a dedicated lithography track system inhibited metal cross contamination and a nitrogen purging resisted oxidation risks. The low temperature operation conditions maintained the device performance without damages. The developed method increased the quantum properties of PbS QDs by 50%.[97] Fourth, the large-scale production of QDs is associated with environmental hazards owing to the toxic heavy metals such as Cd and Pb or toxic organic solvents. Cadmium-free QDs such as carbon QDs, graphene QDs, and silicon QDs have been introduced to minimize environmental hazards associated with the heavy metals and demonstrated comparable optical performance.[98] The European commission has decided to ban cadmium-containing products starting from October 2019, the situation that has led to a dramatic transition in the market of QDs, with the subsequent domination of cadmium-free QDs over 80% of the overall sales of QDs in 2018.[99] Moreover, environment-friendly green synthetic methods have been also developed. Hydrothermal synthesis is an innovative green strategy that has been introduced for the synthesis of carbon QDs. In such a strategy, aqueous conditions and pressurized autoclave vessels are operated at 120–240 °C without incorporating organic solvents. Besides being an environment-friendly strategy, hydrothermal synthesis is economic and produces QDs with competent properties.[100] Additional green methods have been developed such as dry heating, microwave-based synthesis, or those applying recyclable components.[100,101]

## In vivo Issues

In addition to the pharmaceutical and industrial challenges alluded to above, the in vivo application of QDs also encounter hard obstacles. QDs, in principle, have no organ specificity and interact with tissues and cellular membranes in a non-selective manner. In addition, most metallic QDs are associated with intracellular toxicities via oxidative damages to cellular components or interactions with DNA. The risks increase with the use of heavy metals that tend to accumulate in bones without significant elimination from the body such as lead and cadmium. Furthermore, the ultra-fine particle size of QDs increases their premature elimination from the body through renal clearance. PEGylation of QDs has been reported as a common strategy to modulate their biodistribution and to increase their life span in the blood circulation.[102] Modification of QDs with various targeting ligands, polymers, or antibodies has also been reported as a tool to increase their affinity to certain tissues, especially tumors.[103] It has been reported that QDs with an average hydrodynamic diameter less than 5.5 nm are readily excreted from kidneys through glomerular filtration, while fabricating QDs with an average hydrodynamic diameter of 8–10 nm can skip this issue. Choi et al reported that Zwitterionic or neutral organic coatings of QDs can prevent adsorption of serum proteins and modulate the renal clearance of QDs.[104] Moreover, it has been reported that QDs with neutral or negatively-charged surfaces have less susceptibility to glomerular filtration compared to cationic ones. The shape and stiffness of QDs can also be manipulated to modulate their rate of glomerular filtration.[105] On the contrary, various surface modifications have also been developed to enable the clearance of metallic QDs that tend to cause toxic accumulations in the body.[106] Abdellatif has recently reported on the design of excretable metallic QDs via PEGylation combined with active targeting with vapreotide, a selective somatostatin agonist. The results revealed that the modified QDs accumulated in podocytes, specialized epithelial cells covering glomerular capillaries, and suggested that the developed QDs can be excreted from the body through this route.[107]

## QDs versus Other Substitutes

QDs are mostly used as fluorophores for imaging and FACS applications. In this area, organic dyes such as carbocyanines, phycoerythrin (PE), Fluorescein isothiocyanate (FITC), and BODIPY have been widely used as fluorescent labels for the imaging and detection of cellular components, tracking various drug carriers, or labelling the antibodies used for FACS applications.[108] The application of organic dyes has been well-established thanks to their ease of synthesis, cheap prices, commercial availability, and ease of use.[109] Nevertheless, organic dyes have several drawbacks including low molar absorption coefficients, narrow absorption spectra, broad emission spectra, asymmetric emission profiles, short fluorescence lifetime (1–10 ns), and high liability for photobleaching, which increases the difficulty of detection on a single event (ie a single molecule) level.[110] Tandem dyes merging two or more fluorophores such as PerCP/Cy5.5, PE-Cy7, PE-Cy5.5, and APC-Cy7 have been introduced for versatile applications in FACS. In tandem dyes, one fluorophore is being excited by a laser beam from the flow cytometer and the emitted light is transferred to the second fluorophore via a process called Förster Resonance Energy Transfer (FRET) to excite it. The second fluorophore subsequently emits light, which is usually at much longer wavelength than that of the initial laser. Thanks to this approach, a single flow cytometer's laser can excite multiple dyes, while the emitted spectra can be captured on different detectors, which increases the applicability of flow cytometers in detecting multiple fluorophores.[111,112] Despite achieving high success, tandem dyes are still suffering some shortcomings including photobleaching, low thermal stability, and broad emission spectra leading to emission spill over from a detector to another, which requires compensation calculations and limits the compatibility of some fluorophores with each other.[113] QDs possess diverse superior features compared to organic dyes. First, QDs demonstrate broad excitation spectra which facilitates their excitation with various lasers. Second, QDs demonstrate narrow emission spectra which reduces the spill over phenomenon and eliminates the necessity of compensation experiments and complex calculations. Third, QDs show 10-folds longer fluorescence lifetimes compared to organic dyes, with a lower susceptibility to photobleaching. Fourth, the intermittent fluorescence exhibited by QDs facilitates the detection of a single event, which consequently enables the detection of individual cellular components/events with high accuracy. Fifth, QDs possess higher thermal stability, higher brightness, higher molar absorption coefficients, and symmetric emission profiles. Sixth, the optical properties of QDs can be diversely tuned via manipulating their physico-chemical properties and surface chemistry.[110,114] In spite of the above merits, the application of QDs in fluorescence-based processes is still suffering from the shortage of established protocols, the limited knowledge on bioconjugation strategies with various biomolecules especially antibodies, and unsuitability for many enzyme-based fluorescence and luminescence techniques.[110] This area of endeavor is still in need of deep investigation and establishment.

## Clinical Potential of QDs and Future Perspectives

QDs possess several interesting features that make them good candidates for clinical applications. Nevertheless, multiple pharmaceutical, industrial, and technical issues are keeping them away from the clinics so far. In the current section, we attempt to highlight some studies that introduced some promising applications of QDs with a high potential of clinical use. A graphical summary of some of these ideas is presented in Figure 6. Next, we discuss our perspective on the future of QDs and the key aspects that should be considered to improve their clinical applicability.

As discussed previously, QDs showed promising success in bioimaging, which suggests their application in human diagnostic imaging in replacement of classic contrast dyes and radioactive isotopes. QDs can be modified with certain ligands or conjugated to certain antibodies to modulate their accumulation in the desired tissues/organs following intravenous administration, thus enabling visualization of the tissues in question with high efficiency and biosafety compared to classic probes (Figure 6A).[115]

In addition, QDs can be applied for the detection of sentinel lymph node (SLN) metastases that are commonly seen in several tumors, especially breast cancer. Following tumor invasion, tumor cells infiltrate to the sentinel lymph nodes as an early form of metastasis. In the past, all under-arm lymph nodes were being removed with the breast tumor during surgical dissection as a precautionary procedure to prevent metastasis. However, this procedure was associated with several life-long side effects such as edemas and inflammations. This has led to the development of innovative methods for the intraoperative detection of SLNs metastases. Typically, an organic dye called patent blue V is injected in the

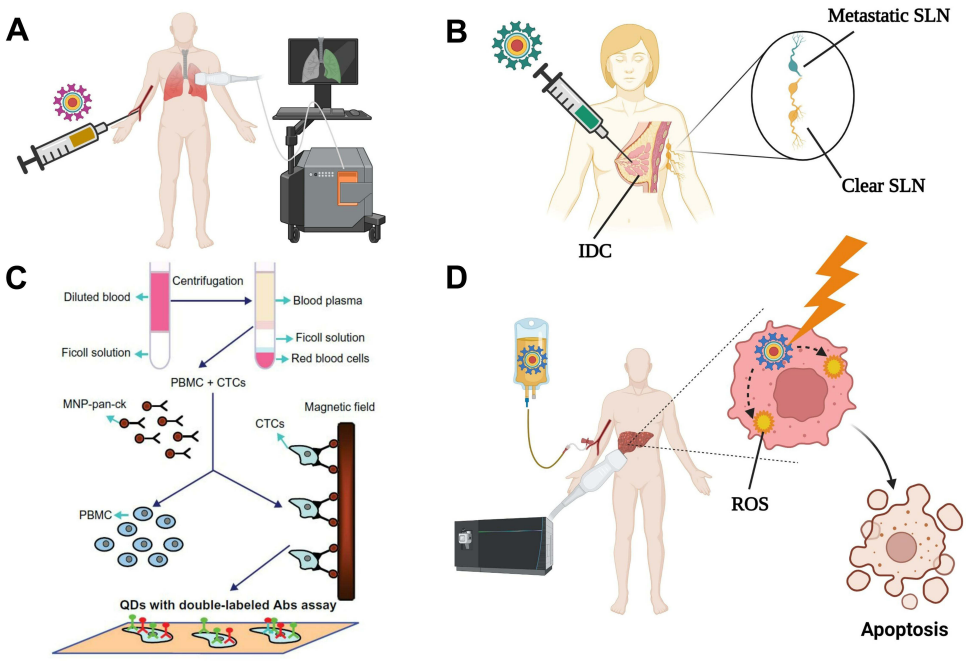



**Figure 6** Some potential applications of QDs in clinics. (**A**) Diagnostic imaging. QDs modified with specific targeting ligands can be injected intravenously to accumulate into the target organ, allowing its visualization. (**B**) Sentinel lymph node (SLN) detection. QDs can substitute the currently-used blue dye or radionuclide methods for the intraoperative detection of SLNs. Following peritumoral injection, QDs diffuse to the affected SLN(s) allowing accurate and safe detection of SLNs metastases. (**C**) Detection of micrometastases. Blood samples from cancer patients are fractioned by gradient centrifugation to collect PBMC and CTCs, followed by their mixing with magnetic nanoparticles that are labeled with anti-pan-ck antibody to enrich lung cancer epithelial cells. The micrometastatic cells conjugated to the magnetic nanoparticles are separated using a magnetic field, incubated with double antibody-labelled QDs, and detected under a fluorescence microscope. The figure (6C) is reproduced from Wang Y, Zhang Y, Du Z, Wu M, Zhang G. Detection of micrometastases in lung cancer with magnetic nanoparticles and quantum dots. Int J Nanomedicine. 2012;7:2315–2324. With a permission from Dove Medical Press, copyright 2012.[81] (**D**) Cancer photodynamic therapy. Following administration of QDs, they tend to accumulate into the tumor site via passive or active targeting. Local irradiation of the tumor site induces the generation of ROS that kill the tumor cells. Created by BioRender.com.
**Abbreviations**: IDC, invasive ductal carcinoma; SLNs, sentinel lymph nodes; CTCs, circulating tumor cells; MNPs, magnetic nanoparticles; Pan-ck, pan-cytokeratin; PBMC, peripheral blood mononuclear cell. ROS, reactive oxygen species.

peritumoral region, then the blue color infiltrates to the affected SLNs, facilitating their detection and guiding the surgeon's decision on which SLNs that need to be removed. This technique has improved the quality of life of huge number of patients and reduced postoperative side effects.[116,117] QDs have high potential to substitute the organic dye during this procedure thanks to their superiority to organic dyes as alluded to above. In addition, QDs can be a safer choice in terms of accumulation and clearance. The principle is outlined in Figure 6B.[9,118]

Cancer metastasis is a serious complication that is commonly seen in most aggressive tumors. Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are common tools that are used in the detection of metastatic lesions in various tissues. Nevertheless, in some cases of aggressive tumors such as lung cancer and breast cancer, metastasis occurs silently with few number of cancer cells circulating in the blood while their number is too low to be detected by the regular methods, which in such a case called micrometastasis. It has been realized that micrometastasis occurs in 30% of breast cancer cases without being detected. Wang et al developed an interesting method for the detection of micrometastases in the blood of lung cancer patients based on QDs. The principle of the method is schemed in Figure 6C. Briefly, blood samples are diluted and mixed with Ficoll solution to facilitate gradient centrifugation. Then, the samples are centrifuged and the peripheral blood mononuclear cells (PBMC) as well as any circulating tumor cells (CTCs) are concentrated at the Ficoll-plasma interface and collected. Magnetic nanoparticles (MNPs) modified with anti-pan-cytokeratin (anti-Pan-ck) antibodies are used to enrich lung cancer epithelial cells, which are then collected by an external magnetic field, incubated with double antibody-labelled CdTe QDs, and detected under a fluorescence microscope. Thanks to this strategy, they could detect micrometastases in the blood of 21 cases out of 26 cases of non-small cell lung cancer patients, which suggested a promising clinical potential.[81]

In addition to the clinical applications suggested above, QDs can be applied in cancer photodynamic therapy as discussed previously. Following administration, QDs can accumulate in the tumor tissue via passive targeting (thanks to their small size, enabling their extravasation at the tumor region by enhanced permeability and retention effect, EPR) or active targeting (in case of ligand-modified QDs). Local irradiation of the tumor site induces the generation of ROS that kill the tumor cells (Figure 6D).[119]

In a very interesting and promising recent study, McHugh et al innovated a method for the personal vaccination recording based on QDs. The prepared QDs composed of CuInSe core and Al-doped ZnS shell and were tuned to emit fluorescence in the near infrared region (NIR) upon excitation by NIR-emitting smartphones. QDs were then incorporated into microparticles and administered intradermally using biodegradable microneedles, along with the inactivated poliovirus vaccine. Thanks to this strategy, the pattern of hypodermal distribution of the injected QDs was exploited to track the vaccination record for at least 9 months post inoculation, with a high resistance to photobleaching that is caused by the exposure to sunlight.[120]

As shown above, QDs hold a great promise for clinical applications, however this is hampered by solid obstacles that need to be addressed. From our point of view, there are key factors that should be considered to improve the clinical translatability of QDs. First, green, environment-friendly, and aqueous solvent-based or biotechnology-based synthetic methods should be adopted to minimize the environmental hazards, improve scalability, and skip unnecessary post-synthetic modifications, which would subsequently decrease the system's intricacy and the production cost. Second, functional coating with smart materials such as pH-responsive polymers and biomaterials with self-homing tissue affinity should replace the current ligand-based modifications to improve both stability and scalability. Third, the concept of heavy metals-free QDs should be adopted to minimize biosafety hazards associated with the heavy metals' accumulation in the body. Fourth, a balance between the body retention and clearance ability of QDs should be achieved via the manipulation of particle size, charge, and surface properties to ensure that the administered QDs can stay in the body for enough time to exert their intended application, while securing their clearance from the body subsequently to avoid toxicity risks. Fifth, an adequate establishment of experimental protocols for the diverse applications of QDs is essential to expand their applications and usage in competition with the classic alternatives which enjoy the wide commercial availability and the presence of well-established protocols. Eventually, continuous research and development of QDs is essential to bring this amazing technology to the clinics for the sake of patients and industry. We believe that this area of endeavor will be fruitful and realize success in the near future.

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## Disclosure

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